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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,060	02/12/2002	David Mu	38002-0024	2406
26633	7590	12/08/2004	EXAMINER GIBBS, TERRA C	
HELLER EHRLMAN WHITE & MCAULIFFE LLP 1666 K STREET, NW SUITE 300 WASHINGTON, DC 20006			ART UNIT 1635	PAPER NUMBER

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/073,060	MU ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 27 September 2004.
- 2a) This action is **FINAL**.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 1-3,9-12,14,22-24,33-35 and 39-43 is/are pending in the application.
- 4a) Of the above claim(s) 4-8,15-21,25-32 and 36-38 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-3,9-12,14,22-24,33-35 and 39 is/are rejected.
- 7) Claim(s) 40-43 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                    | Paper No(s)/Mail Date. _____.   |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input type="checkbox"/> Other: _____.                                   |

**DETAILED ACTION**

This Office Action is a response to Applicants Remarks and Amendment, filed September 27, 2004.

Claims 1-12 and 14-43 are pending in the instant application. Claims 1, 9, 12, 22, and 33 have been amended. New claims 39-43 are acknowledged. Claims 4-8, 15-21, 25-32, and 36-38 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on October 27, 2003.

Claims 1-3, 9-12, 14, 22-24, 33-35, and 39-43 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

*Specification*

In the previous Office Action mailed June 30, 2004, the specification was objected to because the specification at pages 11 and 67 contain embedded hyperlinks and/or other forms of browser-executable code that are impermissible and must be deleted. This objection is withdrawn in view of Applicants Amendment to the Specification to remove embedded hyperlinks and/or other forms of browser-executable from the disclosure.

***Claim Rejections - 35 USC § 112***

In the previous Office Action mailed June 30, 2004, claims 1-3, 9-12, 14, 22-24, and 33-35 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed June 30, 2004.

***Response to Arguments***

In response to this rejection, Applicants argue that the claims have been amended for clarity to incorporate a “detectable” limit for “increase” or “decrease” in amplification and overexpression as set forth by the instrumental detection limit known in the art. Applicants point the Examiner to page 67, lines 9-13 and page 24, lines 3-7.

This argument has been fully considered, but is not found persuasive because first, referring page 67, lines 9-13 disclose the 3'UTR of the hepsin gene, and the coding sequence of genomic DNA clones. It is unclear how this disclosure obviates the instant rejection since it does not lend any information toward Applicants argument or claim amendments. Second, referring to page 24, lines 3-7 discloses the overexpression of a hepsin gene or an increased or elevated level of a hepsin polynucleotide or protein in comparison with a control level of hepsin, is higher. However, this disclosure does not cure the deficiencies of enablement since the instant specification and prior Art demonstrate that specific threshold embodiments must be met and achieved to accomplish the instant methods. For example, see discussion below.

The issue is that the specification and Art demonstrate that specific embodiments must be met to achieve successful and predictable results of the claimed methods. For example, the

instant specification teaches, by way of examples, 5 of 29 ovarian cancer cell lines tested exhibited at least **2.5 fold increase** in hepsin DNA copies (17% frequency); 3 of 8 ovarian tumor cell lines tested exhibited at least **2.5 fold increase** in hepsin DNA copies (38% frequency); and the hepsin gene was found amplified with a frequency of 3% and 6% in tested lung and breast tumors, respectively (see pages 65 and 65, lines 26-31 and 1-13). Also, page 65, lines 28 and 29, indicates that 4 of 5 ovarian cancer cell lines tested exhibited hepsin overexpression in the range of **10 to 100 fold**. Furthermore, in ovarian tumors, 25 of 29 tested exhibited at least **5 fold increase** in hepsin mRNA expression compared to normal, while 5 of 9 ovarian tumor cell lines tested exhibited at least **5 fold increase** in hepsin mRNA expression compared to normal. In prostate tumors, 8 metastatic prostate tumors overexpressed hepsin mRNA, in the range of **7.7 to 89 fold** in the tumor tissue (see page 66, lines 16-26). The Art teaches hepsin overexpression was above the mean normal level by **+2 SD (2+)** or by **+4 SD (4+)** (see Tanimoto et al. Cancer Research, 1997 Vol. 57:2884-2887, at Table 1). Magee et al. (Cancer Research, 2001 Vol. 61:5692-5696) teach prostate tumor samples tested exhibit a **>3 fold increase** in hepsin expression relative to control/benign samples (see Table 1). Stephan et al. (Journal of Urology, 2004 Vol. 171:187-191) teach in 48 patients, hepsin over expression was more than **10-fold** in cancerous prostate tissue compared to normal prostate tissue (see Abstract).

As discussed in the previous Office Action mailed June 30, 2004, based on the guidance in the specification and what is taught in the Art, the skilled artisan would conclude that to practice the claimed methods, specific threshold embodiments must be met and achieved.

These specific threshold embodiments are not required by the instant claims and one of ordinary skill in the art would need to undergo undue trial and error experimentation to

determine what threshold parameters would need to be met before practice of the claimed methods can be successfully achieved. This undue experimentation would include the determination of specific threshold parameters, including percent folds of hepsin reduction, amplification, duplication, or overexpression, which would be significant to result in the diagnosis of cancer or efficacy of therapeutic treatment in a mammal as claimed. Given the art-recognized requirement for such parameters, this determination would not be routine and would require undue trial and error experimentation.

***Claim Rejections - 35 USC § 102***

In the previous Office Action mailed June 30, 2004, claims 33-35 remained rejected under 35 U.S.C. 102(b) as being anticipated by Zacharski et al. (Thromb Haemost, 1998 Vol. 79:876-877). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed June 30, 2004.

***Response to Arguments***

In response to this rejection, Applicants argue that the claims have been amended to recite an element that “hepsin is amplified or overexpressed in tumor cells [lines] compared to normal cells”, which is not present in Zacharski et al.

This argument has been fully considered, but is not found persuasive because the Examiner has reassessed the disclosure and teachings of Zacharski et al. Zacharski et al. disclose

immunohistochemical techniques using purified polyclonal monospecific anti-hepsin antibodies to study hepsin expression in renal cell carcinoma and normal renal tissues *in situ* (see page 876, second column, last paragraph and Figure 1). Zacharski et al. further disclose staining of normal tissue and other tumor types, including ovarian cancer, adenocarcinoma, and squamous cell carcinoma of the lung (see page 877, first column). The data of Zacharski et al. is stored in the Thromb Haemost Journal in paper format.

It is noted that the instant specification at page 41, lines 19 and 20, discloses, "A methodology for determining the copy number of the hepsin gene in a sample is *in situ* hybridization". The Examiner acknowledges that in the previous Office Action mailed June 30, 2004, at page 9, last paragraph recites, "While Zacharski et al. do not suggest that hepsin is amplified or overexpressed in tumor lines compared to normal cell, these parameters are not required by the instant claims". The Examiner would like to retract this statement as Zacharski et al. clearly teach that hepsin is amplified or overexpressed in tumor lines compared to normal cells. For example, Zacharski et al. teach, "we applied immunohistochemical techniques using purified polyclonal monospecific anti-hepsin antibodies to study hepsin expression in seven cases of renal cell carcinoma (RCC), in normal tissues, and in tissues from several other tumor types" (see page 876, second column). Zacharski et al. further teach, "Specific staining for hepsin localized exclusively to tumor cell membranes was observed in all seven cases of RCC (Figure 1)" (see page 876, second column). Zacharski et al. further teach, "the lack of staining in normal kidney tissue suggests that hepsin expression may be a manifestation of the neoplastic phenotype in RCC" (see page 877, first column). Therefore, it is evident from the disclosure of Zacharski et al. that hepsin is amplified or overexpressed in tumor lines compared to normal cell.

Claims 33-35 are drawn to a method for diagnosing a cancer in a mammal, comprising detecting hepsin protein expression by contacting a biological subject from a region of the mammal that is suspected to be precancerous or cancerous with anti-hepsin antibody. Zacharski et al. teach this one method step, and therefore, Zacharski et al. anticipate claims 33-35.

After careful reconsideration of the claims, a new grounds of rejection is made of record as presented below:

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanimoto et al. (Cancer Research, 1997 Vol. 57:2884-2887).

Claims 1-3 are drawn to a method for diagnosing a cancer in a mammal comprising a method for diagnosing a cancer in a mammal, comprising detecting and measuring hepsin gene copy number in a biological subject from a region that is cancerous and comparing the hepsin mRNA transcript to a control, wherein the biological subject is selected from ovarian, prostate, breast, or lung tissue and wherein the data is stored electronically or in a paper format. Claim 39 is dependent on claim 1 and includes all the limitations of claim 1, with the further limitation, wherein the detectable increase in amplification is about 2.5 fold.

It is noted that the instant specification at page 42, lines 16-18, discloses "amplification-based assays also can be used to measure the copy number of the hepsin gene. In such assays, the corresponding hepsin nucleic acid sequences act as a template in an amplification reaction (for example, Polymerase Chain Reaction or PCR). In a quantitative amplification, the amount of amplification product will be proportional to the amount of template in the original sample. Comparison to appropriate controls provides a measure of the copy number of the hepsin gene."

Tanimoto et al. disclose the identification of overexpressed hepsin in ovarian carcinomas compared to normal ovaries from patients (see Abstract). Tanimoto et al. disclose the evaluation of hepsin mRNA expression in ovarian tumors, performed using quantitative PCR (see Figure 1). The data of Tanimoto et al. is stored in the Cancer Research Journal in paper format.

Therefore, Tanimoto et al. anticipate claims 1-3.

#### ***Claim Objections***

Claims 40-43 are objected to as being dependent upon rejected base claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1635

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg  
December 1, 2004

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